

REVIEW ARTICLE

Diffusion-weighted magnetic resonance imaging in neck lymph adenopathy

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Abstract

In patients with head and neck squamous cell carcinoma (SCC), nodal metastases are an adverse prognostic factor compromising long term patient survival. Therefore, accurate detection of regional nodal metastases is required for optimization of treatment. Computed tomography (CT) and magnetic resonance imaging (MRI) remain the primary imaging modalities for locoregional staging of head and neck SCC. Next to evaluation of the primary tumour, both modalities facilitate detection of non-palpable lymph nodes (LN). However, both modalities rely on size-related and morphological criteria to differentiate between benign and malignant lymph nodes, decreasing the sensitivity for detection of small metastases. Diffusion-weighted MRI (DW-MRI) measures differences in tissue microstructure, based on the random displacement of water molecules. The differences in water mobility are quantified using the apparent diffusion coefficient (ADC), which has an inverse relationship with tissue cellularity. As such the technique is able to differentiate between tumoral tissue and normal or necrotic tissue. The added value of DW-MRI to conventional imaging for staging of lymph nodes in head and neck cancer is discussed, before and after treatment. The possible consequences regarding therapeutic management are outlined.

Keywords: Neck lymph adenopathy; head and neck radiology; neck lymph nodes; magnetic resonance imaging.

Introduction

Squamous cell carcinoma (SCC) is one of the most frequent tumours in the head and neck region for which chemo-radiotherapy (CRT) and surgery are curative treatment options. Metastatic involvement of neck lymph nodes is a frequent finding for this tumour type and has a major negative prognostic impact on patient survival^[1]. As such, accurate detection of nodal metastases is mandatory to optimize the treatment plan. Thereby, therapeutic efficacy needs to be outweighed against potential therapeutic induced morbidity or complications.

Computed tomography (CT) and magnetic resonance imaging (MRI) are the primary diagnostic modalities for locoregional staging of SCC. However, their reliance on morphological and size-related criteria bears some inherent disadvantages. Both techniques may fail to detect

small metastatic deposits and have difficulty in differentiating between metastatic and inflammatory enlarged lymph nodes; a problem that is not always solved by [¹⁸F]fluorodeoxyglucose (FDG)-positron emission tomography (PET). This is in part due to the low spatial resolution and the variable physiological FDG-uptake in anatomical structures and inflammatory lymph nodes^[2].

Although effort is done to increase the diagnostic accuracy of MRI by the use of ultrasmall superparamagnetic iron oxide particles (USPIO), the results remain somewhat contradictory and its role in post-treatment evaluation of nodal disease has so far not been evaluated^[3,4].

Diffusion-weighted MRI (DW-MRI) is a functional technique which characterizes tissue by differences in microstructure, based on the random displacement of water molecules. The differences in water mobility are quantified by using the apparent diffusion coefficient (ADC). This ADC reflects the signal loss on the

DW-images with increasing b -value and shows an inverse correlation with tissue cellularity^[5].

The aim of this paper is to discuss the biological and technical background of DW-MRI and the potential value of DW-MRI in conventional imaging for staging of lymph nodes in head and neck cancer, before and after treatment. The possible consequences regarding therapeutic management are outlined.

Imaging technique and image analysis

Echo-planar (EPI) based DW-MRI faces many challenges to achieve acceptable diagnostic quality in head and neck imaging. The major advantage – and reason – for using EPI-based DW-MRI is the inherent rapidity, which makes it easier to scan large volumes in a short period of time. Another important advantage – mandatory for evaluation of small lesions – is that the technique is able to provide a substantially shortened echo-time resulting in a high signal-to-noise ratio (SNR). The disadvantage of this gradient based sequence, however, is the susceptibility and fat-shift artefacting, especially when air–tissue interfaces are present. This may lead to image distortion and loss of SNR and ultimately, non-diagnostic image quality. Technological improvements have largely overcome these problems, by combining dedicated coils, parallel imaging and dedicated or manual shimming^[6]. As such the sequence can routinely be integrated in head and neck MRI. In our department, a combination of a standard head coil and 2-channel

dedicated surface neck coil is used for head and neck DW-MRI. The sequence is acquired in the transverse plane with 44 slices, including the neck from the skull base to the thoracic inlet in order to cover all nodal stations. Furthermore, the sequence consists of a bandwidth of 1502 Hz/pixel, 4 mm slice thickness, 0.4 mm intersection gap, Field-of-view $20 \times 25 \text{ cm}^2$, matrix of 104×128 , repetition time (TR)/echo-time (TE) = 7100 ms/84 ms, 3 averages and a pixel resolution of $2.0 \times 2.0 \times 4.0 \text{ mm}^3$. Six b -values are applied ($b = 0, 50, 100, 500, 750$ and 1000 s/mm^2). All diffusion-sensitizing gradients are applied in 3 orthogonal directions and combined to create a 3-scan trace. For head and neck DW-MRI, the necessary high SNR can be obtained by decreasing the TE as much as possible. This is in part determined by the inherent gradient strength of the MRI system, which should be sufficient on the 1.5 and 3 T systems currently in use. In addition, a high bandwidth, with the resulting shorter echo-spacing, can be implemented to further shorten TE and acquisition time and increase the SNR.

Manual shimming should also be considered as an important factor and judicious localization should lead to an improved image quality reducing fat-shift and distortion artefacts^[6]. In our experience, a shim covering the spine and muscles of the neck while avoiding moving or air-containing structures offers optimal imaging quality (Fig. 1). Evidently, shim-optimization may slightly differ depending on the MRI system and coil type used and may be established for each centre separately.

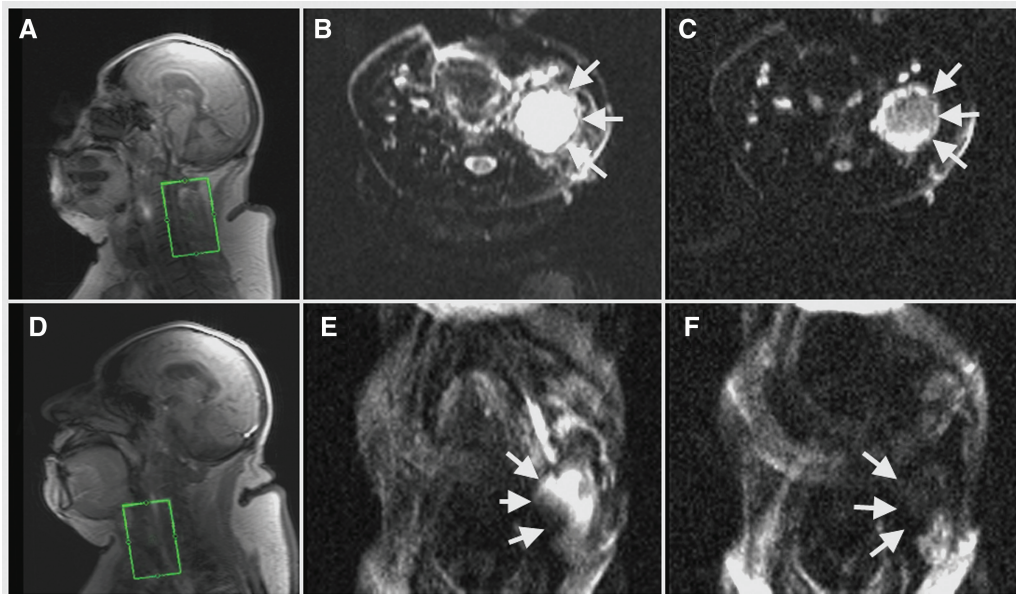


Figure 1 The effect of manual shim-optimization is shown in a representative patient, presenting with a large necrotic adenopathy in left level 2 (arrows): (A) the shim-box is positioned in the area of the spine and posterior muscles of the neck, with (B,C) only limited artefacting visible on the b_0 and b_{1000} images. (D) The shim-box is erroneously placed on the larynx, resulting in severe fat-shift and distortion artefacts. (E,F) The large necrotic adenopathy (arrows) is barely visible on the native b_0 images and not visible on the b_{1000} images.

The ability to probe tissue water mobility depends on the addition of two equally large but opposite gradient pulses. The first gradient pulse induces a phase shift of water molecules which will be followed by an incomplete rephasing after the second gradient pulse, with a magnitude depending on the mobility of the water molecules. This incomplete rephasing will result in a net signal loss on the sequences with increasing diffusion sensitivity. The latter is influenced by the b -value, which determines the effect of gradient strength on diffusion sensitivity^[7].

At our institution, 6 b -values ranging from 0 to 1000 s/mm² are usually applied. Although relatively more time consuming, the inclusion of a high number of b -values holds several advantages. A higher number of b -values improves the accuracy of the ADC calculation, minimizes the influence of movement and noise propagation. This enables the characterization of lesions as small as 4–5 mm. A dedicated head and neck DW-MRI sequence at 1.5 T using 48 slices, 4 mm slice thickness and 6 b -values ranging from 0 to 1000 s/mm² typically takes 5–6 min. If the number of b -values is reduced to 3, the scanning time can easily be halved, and thin section imaging remains possible.

Although imaging is technically feasible in the head and neck, a number of issues still need to be dealt with. Further studies should focus on standardization of technique and image interpretation. Especially the choice of b -values is pivotal as it has major influence on the ADC calculation. Most likely the variety of b -value settings used for the ADC calculation in different studies is the major cause of the variable results reported^[8,9]. Therefore, agreement on imaging standardization should be a major issue for the near future, especially because nodal differentiation is highly dependent on quantitative analysis with ADC calculation. Both benign and malignant lymph nodes will show an increased but variable SI on high b -value images and cannot be differentiated using the native images alone.

Quantitative analysis can be performed by drawing regions of interest (ROIs) over the lymph nodes on the separate native b -value images and calculating the ADC from the SI on the consecutive b -value images^[10]. Contrary to the ADC map, lymph nodes can easily be identified on the native DW-MRI images due to the higher contrast-to-noise ratio (CNR).

In general, solid adenopathies are evaluated placing an ROI over the entire volume of the lymph node. In necrotic adenopathy, if obvious solid and necrotic components are visible, ROIs are placed on the separate tissue portions^[11].

Until now, no studies have been performed evaluating the influence of small ROI size on diagnostic accuracy of DW-MRI. In our experience and in correlation with the findings in the literature, tumoral depositions in the head and neck or lymph nodes as small as 4 mm have sufficient SNR on the native b -value images for reliable ADC calculation^[12,13].

Pre-treatment imaging

Different studies have reported on the ability of DW-MRI to differentiate metastatic from benign lymph nodes^[8,9]. Higher sensitivity and specificity than anatomical imaging modalities have been shown. Moreover, preliminary results suggest the possibility for the detection of subcentimetric nodal metastases in the head and neck^[14].

The pronounced difference on DW-MRI between tumoral and non-tumoral lymph nodes can be explained by the microstructural differences between metastatic squamous cell carcinoma and lymphoid tissue. SCC shows a multitude of enlarged cells with clear morphological heterogeneity and increased mitosis. These features diminish free water movement resulting in a low ADC. This is in contrast with the normal nodal architecture, which consists mainly of small lymphoid cells ordered in scattered germinal centres and vessel-like sinusoids. These features can be expected to correlate with an enlarged interstitial space, facilitation of water movement and a high ADC.

The dependency of microstructural changes for nodal differentiation also cautions for potential pitfalls in image interpretation. In necrotic metastases, for instance, the low amount of intact tumoral cells can result in a falsely increased ADC, potentially leading to misdiagnosis. This can be overcome by correlation of the DW-MRI images to the contrast-enhanced MRI sequences which have a high accuracy for detection of necrotic metastases^[15]. As previously mentioned, with the DW-MRI sequences in current use, small viable tumoral parts can be differentiated from necrotic tissue by visual inspection of b_0 and b_{1000} images, allowing correct diagnosis^[9].

False positive findings on DW-MRI are mainly caused by nodal reactivity, which is characterized by a homogeneous lymphoid infiltration, organized in a multitude of germinal centres and the presence of fibrous stroma^[6]. These histological features also increase microstructural barriers and can decrease ADC to a level similar to that of metastatic lymph nodes. Careful correlation with nodal morphology may be helpful to avoid misdiagnosis as the presence of a nodal fat-containing hilus is highly indicative for the absence of metastatic disease^[16]. In our experience, such reactive nodal changes do not appear to have major clinical impact as they are usually found in the neighbourhood of nodal metastases.

Next to the differentiation of benign from metastatic lymph nodes, studies indicate that DW-MRI may be useful for differentiating separate histological tissue types in tumoral adenopathies^[8,9,17]. These studies have shown a significantly higher ADC in SCC than in lymphoma and – less pronounced – nasopharyngeal carcinoma (NPC). Moreover, DW-MRI appears to yield acceptable accuracy to differentiate SCC from lymphoma.

The different ADC of SCC compared to the other tumour types may be related to differences in tissue

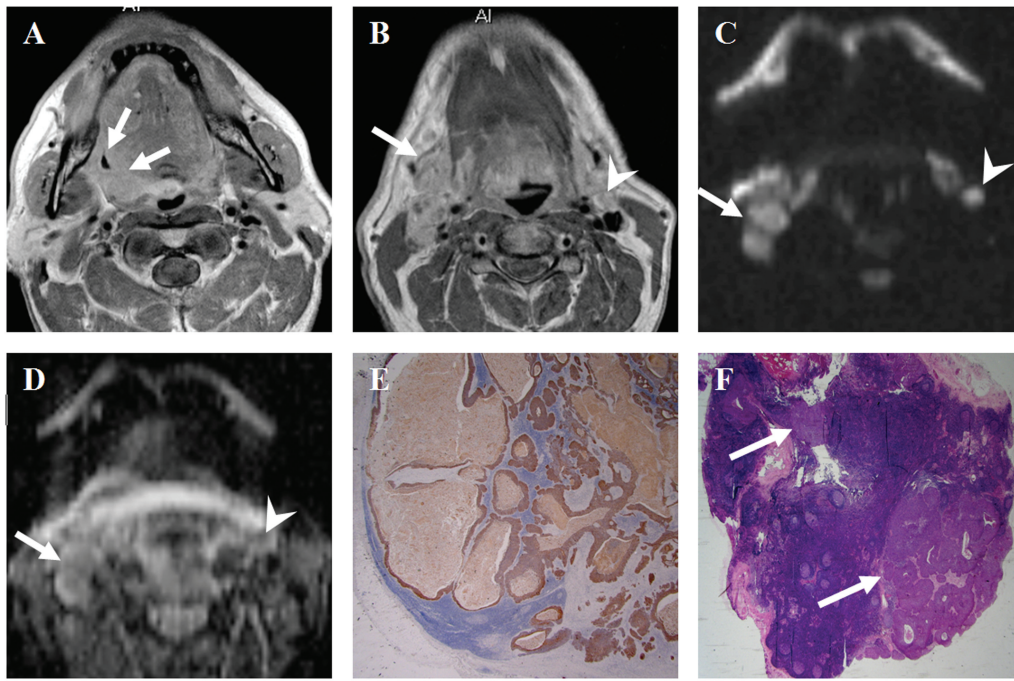


Figure 2 (A) Patient presenting with a right-sided oropharyngeal tumour (arrows). (B) Enlarged adenopathy is visible at the right side (arrow), while a small lymph node is visible in the left neck (arrowhead). (C) The small lymph node on the left (arrowhead) shows hyperintensity on the b_{1000} diffusion-weighted image similar to the adenopathy on the right (arrow). (D) ADC of right-sided adenopathy (arrow) shows a borderline value of $0.00095 \text{ mm}^2/\text{s}$, while the left-sided lymph node (arrowhead) has a low ADC of $0.00063 \text{ mm}^2/\text{s}$. (E) Histopathology of the right-sided adenopathy using immunohistochemical staining shows partially necrotic metastasis. (F) Histopathology with haematoxylin–eosin staining also confirms metastatic deposits in the left sided lymph node.

cellularity, size and/or constitution of the extracellular space rather than in differences in microperfusion or intranodal micronecrosis. The overlap of ADC between NPC and lymphoma is probably due to the closer histological similarity of NPC to lymphoma than to SCC^[17].

However, a number of issues remain unclear and warrant further research. The results of the studies mentioned above may only be applicable to non-Hodgkin's lymphoma, as the higher ADC found in Hodgkin's lymphoma may induce higher overlap of ADC with SCC^[19,17]. Moreover, as the ADC value in SCC may vary depending on tumour differentiation, overlap can occur between poorly differentiated SCC and lymphoma, which may also negatively impact on diagnostic accuracy^[6].

The ability to detect nodal metastases based on microstructural changes may give DW-MRI a complementary role in the pre-treatment staging of head and neck SCC, where CT and conventional MRI remain the primary imaging modalities in the initial locoregional staging. Next to determination of the extent of the primary tumour, both modalities often provide sufficient information on nodal metastatic spread in the presurgical setting. The use of size-related and morphological criteria, however, harbours some inherent disadvantages regarding the detection of small nodal metastases and the differentiation of inflammatory enlarged

lymph nodes^[18]. Therefore, both techniques lack sufficient accuracy and neck dissection cannot be avoided in the clinically negative neck. Furthermore, the difficulties in differentiating small nodal metastases may hamper the detection of small contralateral or skip metastases.

The higher sensitivity of DW-MRI compared to conventional MRI can improve the detection of metastatic lymph nodes at clinically relevant sites (Fig. 2). The detection of contralateral and retropharyngeal lymph node metastases has tremendous impact on patient management, locoregional outcome and patient survival^[19]. In different studies, a high negative predictive value (NPV) with DW-MRI, ranging from 82 to more than 90%, has been described^[8,9]. In combination with the ability to detect small nodal metastases, down to 4 mm^[13,14], DW-MRI may help to limit the extent of neck dissection required or be useful for radiotherapy (RT) planning.

As such, DW-MRI can provide additional information to conventional imaging for detection of small nodal metastases in patients with oral cancer, who are potentially eligible for limited neck dissection in selected cases (Fig. 3). The improved sensitivity in combination with the high NPV may also be of use in RT planning, as close conformity of the radiation target volume to the imaging-determined tumour extent can decrease treatment-induced toxicity. If confirmed in larger studies,

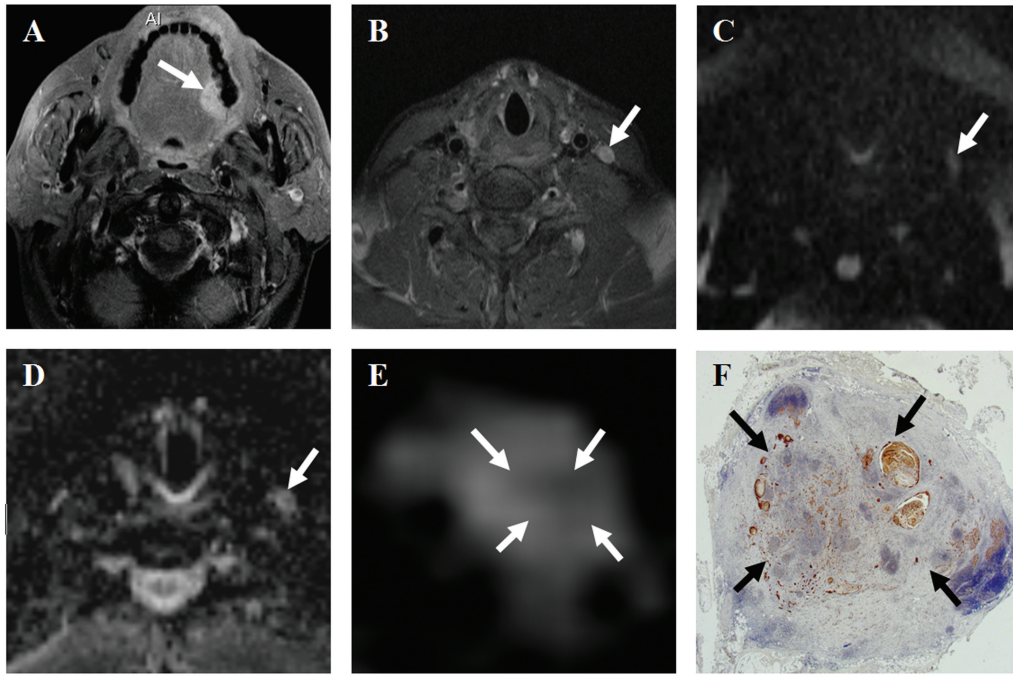


Figure 3 (A) Patient presenting with a T2 tumour of the left oral tongue (arrow). (B) Small, rounded lymph node with heterogeneous contrast-enhancement in the left neck level III (arrow). (C) The lymph node shows a hyperintense signal on native b_{1000} diffusion-weighted image and corresponds to (D,E) a low ADC of $0.00087 \text{ mm}^2/\text{s}$. (F) Histopathological examination using immunohistochemical staining shows a metastatic deposit in the centre of the lymph node.

the increasing ability of DW-MRI to detect and exclude small volume metastatic disease raises the question if residual metastatic deposits too small for detection may be eligible for treatment with de-escalated doses. For instance, if the risk for contralateral metastases can be minimized sufficiently, DW-MRI may help to increase the number of patients eligible for parotid sparing RT, where the contralateral neck is irradiated with de-escalated doses^[20]. However, as for all imaging modalities, a number of micrometastatic depositions are likely to remain undetected and potential applications should be balanced against relevant clinical risk factors for regional tumour spread^[21,22].

Post-treatment imaging

New developments such as multifractionated RT in combination with chemotherapy have led to a substantial gain in locoregional control and overall survival in advanced head and neck cancer^[23]. The management of the post-RT neck, however, remains a challenging issue as there is no clear consensus over the need for a planned post-RT neck dissection in patients who had positive nodes before RT. Modern CRT is able to eradicate nodal disease, even in advanced stages of disease. Although a post-RT neck dissection can improve local control rates, this is often achieved at the cost of a high number of histopathologically negative neck dissections^[24]. As a number of patients are undergoing unnecessary salvage surgery,

the potential benefit of such a surgical procedure should be outweighed against the iatrogenic morbidity for the patient.

The accuracy of currently used imaging modalities may be diminished by post-RT inflammation and fibrosis, especially in the early phase after CRT. Similar to the pre-treatment setting, conventional MRI and CT are limited by the size-related criteria for the detection of small residual tumoral depositions and the differentiation of persistently enlarged lymph nodes^[18]. The variable inflammatory changes and often small volume of residual tumoral depositions may lead to false positive and false negative findings on FDG-PET in the early post-RT phase^[25].

Two independent studies using DW-MRI have described similar high accuracy for the detection of post-treatment recurrence in the head and neck^[11,12]. In both studies, a significantly lower ADC was found for tumour recurrence than for post-operative and post-radiotherapeutic tissue alterations like inflammation, necrosis and fibrosis. The higher accuracy obtained in the post-radiotherapeutic setting compared to pre-treatment nodal imaging can probably be explained by the more pronounced microstructural changes between metastatic depositions and irradiated lymph nodes. Post-radiotherapeutic alterations consist mainly of fibrosis, inflammatory tissue and necrosis and show less cellularity than a normal lymph node. Therefore, the ADC can be expected to be higher in benign post-RT

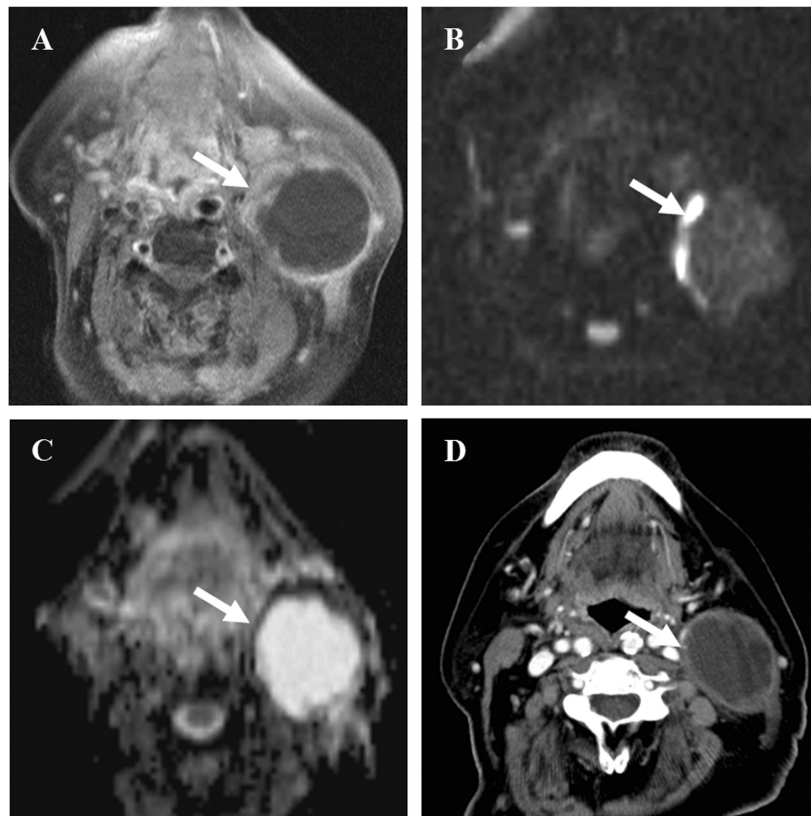


Figure 4 (A) MRI examination 3 weeks after end of chemo-radiotherapy shows a persistent necrotic adenopathy on the left (arrow). (B) On the native b_{1000} diffusion-weighted image, strongly hyperintense soft tissue deposits are present in the nodal periphery, correlating to (C) a low ADC of $0.00108 \text{ mm}^2/\text{s}$. These findings are suggestive of persistent intact tumoral tissue in the adenopathy. (D) Follow-up CT at 6 months showed persistent left-sided nodal disease. Due to inoperability, chemotherapeutic treatment was initiated.

alterations, showing higher contrast with a persistent or recurrent metastatic lymph node. DW-MRI appeared to be especially useful in the differentiation of persistently enlarged inflammatory and tumoral lymph nodes with equivocal findings on CT, conventional MRI or FDG-PET^[12].

As such, DW-MRI could be used in the differentiation of persistently enlarged lymph nodes after completion of CRT (Figs. 4 and 5). Due to its high negative predictive value, DW-MRI may help in the post-RT follow-up by obviating invasive diagnostic procedures or surgical intervention. In this setting, DW-MRI should primarily be seen as an additional imaging technique complementing clinical and conventional imaging findings. Further studies are required to determine appropriate clinical indications and potential clinical impact.

A future potential application, which is currently being researched, is to use DW-MRI as a predictive marker during and early after CRT for head and neck cancer. Unlike FDG-PET, one of the major advantages of DW-MRI is the insensitivity to inflammatory changes, making the technique suitable for tumour imaging during CRT. Changes depicted by DW-MRI have been shown to correlate with treatment response in CRT of

rectal cancer and the technique has been validated as a marker for early treatment response in brain cancer^[26,27].

If early treatment induced changes in the microstructural integrity of head and neck SCC on DW-MRI correlate with the eventual post-treatment outcome, the technique may be useful as a biological marker and may help to tailor the treatment plan to the patient's individual response.

Conclusion

Due to its ability to probe the tumoral microstructure, DW-MRI offers an alternative approach in head and neck cancer imaging, providing complementary information to anatomical imaging modalities.

Current limitations such as non-straightforward image interpretation and lack of sequence standardization require further studies before the technique can be used for routine clinical applications. However, as the technique is easy to integrate in standard imaging protocols, continuous progression of widespread research should lead to improved diagnostic accuracy.

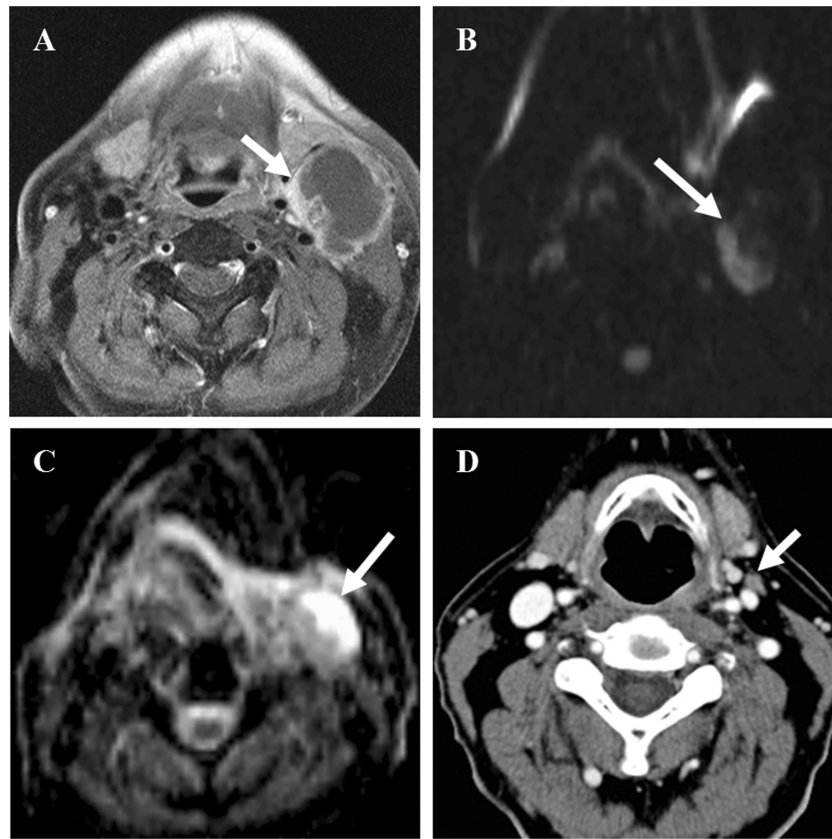


Figure 5 (A) MRI examination 3 weeks after end of chemoradiotherapy shows a persistent necrotic adenopathy on the left (arrow). (B) The lymph node shows only faint heterogeneous hyperintensity on the native b_{1000} diffusion-weighted image correlating to a (C) high ADC of $0.00155 \text{ mm}^2/\text{s}$. These findings are highly suggestive of complete necrosis. (D) Follow-up CT at 24 months shows complete regression of the lymph node.

Most likely, DW-MRI will not be able to tackle all diagnostic problems and the technique should be considered as a problem-solving technique set by strict clinical indications. However, if applied in the appropriate setting, DW-MRI will very likely be of additional use, for example in nodal characterisation in the pre- and post-therapeutic situation.

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